REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow. No amendments have been made.

Withdrawn Rejections

Applicant thanks the Examiner for withdrawal of the rejections as stated in the Office Action, as well as for his acceptance of the drawings.

Claim Rejections - U.S.C. § 103

Terman in view of Ruoslahti

Claims 1 and 3 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Terman (US 6,340,461), in view of Ruoslahti (US 6,180,084). Specifically, the Examiner asserts that Terman discloses a pharmaceutical composition comprising, in addition to a carrier, a superantigen and immunotherapeutic complex, comprising a galactose-α-1,3-galactose xenograft antigen as the immunotherapeutic portion, and further comprising a targeting portion using an antibody. The Examiner further asserts that one of skill in the art would substitute the NGR peptide of Ruoslahti in place of the antibody since NGR peptides were disclosed to target tumor vasculature. Applicants respectfully traverse this rejection.

The Supreme Court recently reaffirmed the *Graham* factors for determining obviousness in *KSR Int'l Co.* v. *Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966). In accordance with these factors, to establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or

suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met. Additionally, although the Examiner correctly notes that each reference cannot be properly attacked individually, the teachings of each reference must be carefully analyzed to arrive at the combined teaching as a whole.

The present claims are directed to a pharmaceutical composition comprising (a) a carrier portion, (b) a targeting portion, wherein said targeting portion comprises a targeting peptide that targets cancerous cells, tumor vasculature or neovasculature, and (c) an immune response triggering portion, wherein said immune response triggering portion is galactose-α-1,3-galactose which triggers a complement mediated hyperacute immune response, and wherein neither the carrier portion of (a) nor the targeting portion of (b) is an antibody or antibody fragment. Applicant asserts that the combination of cited references do not arrive at the claimed invention, nor do they provide the surprising result that antibody-targeting actually inhibits the complement-mediated hyperacute immune response, and thus cannot render the claimed invention obvious.

First, to combine Ruoslahti with Terman and arrive at the present invention, not only would one have substitute the targeting moiety of Terman, but also one of skill would be required to delete the superantigen portion of the Terman complex. Terman is solely directed to using superantigens, such as enterotoxins, in combination with immunotherapeutic moieties, which can be galactose-α-1,3-galactose. The enterotoxin portion of the Terman is described as providing key immunogenic responses, as discussed, *inter alia*, column 8, line 32 to column 9, line 17. These responses, which are T cell mediated, are not found in the present invention, which uses the complemented-mediated hyperacute immune response. Thus, a person of skill in the art would have no reason to delete this important portion of the Terman complex to arrive at the present invention, as the superantigen is described as being an essential feature. Ruoslahti provides no such incentive to remove the superantigen as it merely discloses the NGR peptide. Combining Ruoslahti with Terman still includes the superantigen domain not present in the claimed invention.

The Examiner is reminded that elements of the cited references cannot be modified without some explicit reason provided in the art. "One cannot use hindsight reconstruction to

pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1975 (Fed. Cir. 1988). Further, "[a] reference may be said to teach away when a person of ordinary skill, upon reading reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). A person of skill in the art would necessarily conclude from reading Terman and without contradiction from Ruoslahti that a superantigen domain is critical to the desired result. Therefore, the cited references do not teach each and every element of the claimed invention as they actually require additional elements for success.

Second, the claim limitation that neither the carrier nor the targeting portion can be antibody-derived is critical as it has surprisingly been found that use of an antibody in the present invention inhibits the complement mediated hyperacute immune response, as discussed in Example 3, specifically paragraph 61, of the specification and shown in the data of Figure 2. This characteristic of antibody-targeting being unsuitable for the present inventive composition was heretofore unappreciated and discovered by Applicant. It should be noted that Terman merely speculates that the use of antibody-targeting in conjunction with the galactose-α-1,3-galactose-superantigen complex would trigger the hyperacute rejection process as an additive effect to T cell stimulation. No data showing such an effect is provided. A person of skill in the art, reading Terman, would conclude that using an antibody to target galactose-α-1,3-galactose complexes would be successful, when Applicants have clearly shown that it would not be.

Because the cited combination of references teach the necessity of using the superantigen moiety as well as the success of using antibody targeting, they cannot anticipate the present invention. Therefore, Applicants respectfully request that the rejection be withdrawn.

Terman in view of Ruoslahti and in further view of Corti

Claim 2 remains rejected under 35 U.S.C. §103(a) as being unpatentable over Terman (US 6,340,461), in view of Ruoslahti (US 6,180,084), and in further view of Corti (WO 01/61017). Specifically, the Examiner alleges that Corti adds to the previously cited combination of Terman and Ruoslahti the use of human serum albumin (HSA) as the carrier. Applicants respectfully traverse this rejection.

The deficiencies of Terman and Ruoslahti discussed *supra* remain applicable. Corti uses HSA as a carrier for a NGR-TNF complex. The Examiner asserts that one of skill in the art would be motivated to use the same carrier in the present invention because HSA did not appear to alter the T-cell immunogenecity of the NGR-TNF complex. However, Corti does not remedy the deficiencies of the complexes of Terman and Ruoslahti as it merely specifies a type of carrier to be used. It does not provide any guidance as to the removal of the superantigen domain of Terman, nor does it teach the surprising effect that antibody portions have on complement-mediated responses. Thus, the cited combination of references cannot render the present invention obvious. Therefore, Applicants respectfully request that the rejection be withdrawn.

Terman in view of Ruoslahti and in further view of Patierno

Claims 10-16 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Terman (US 6,340,461), in view of Ruoslahti (US 6,180,084), and in further view of Patierno (US 6,288, 039). Specifically, the Examiner alleges that Patierno teaches kits for treating breast cancer. Applicants respectfully traverse this rejection.

The deficiencies of Terman and Ruoslahti discussed *supra* remain applicable. Patierno relates to a different invention altogether, and its disclosure of the use of kits cannot overcome the deficiences of Terman and Ruoslahti. It does not provide any guidance as to the removal of the superantigen domain of Terman, nor does it teach the surprising effect that antibody portions have on complement-mediated responses. Thus, the cited combination of

references cannot render the present invention obvious. Therefore, Applicants respectfully request that the rejection be withdrawn.

Terman in view of Ruoslahti and Patierno, and in further view of Corti

Claim 18 remains rejected under 35 U.S.C. §103(a) as being unpatentable over Terman (US 6,340,461), in view of Ruoslahti (US 6,180,084) and Patierno (US 6,288,039), and in further view of Corti (WO 01/61017). Again, the Examiner uses Corti to specify HSA as the carrier combined with the complexes of Terman and Ruoslahti, in the context of the kit of Patierno. Applicants respectfully traverse this rejection.

The deficiencies of Terman and Ruoslahti discussed *supra* remain applicable. For the same reasons stated above, the combination of Corti and Patierno do not overcome these stated limitations. They do not provide any guidance as to the removal of the superantigen domain of Terman, nor do they teach the surprising effect that antibody portions have on complement-mediated responses. Thus, the cited combination of references cannot anticipate the present invention. Therefore, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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